Application No. 09/550,103
Filed: April 14, 2000
Group Art Unit: 1647

REMARKS

Claims 1-9 are pending in the present application. Claims 1-4 are withdrawn from consideration as non-elected claims. Accordingly, claims 5-9 are pending upon entry of the present amendment.

Support for any amendments to the claims can be found throughout the specification and claims as originally filed. No new matter has been added.

Any amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Claim Rejection - 35 U.S.C. §112, First Paragraph

Claims 5-9 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that while the specification is enabling for a method of "identifying therapeutic agents for neuropsychiatric diseases involving the D4 receptor and in which phospholipid methylation has been shown to be affected, does not reasonably provide enablement for agents or processes involving other neuropsychiatric diseases in which a clear link from the D4 receptor to phospholipid methylation has not been established."

Applicant respectfully traverses the foregoing rejection.

The presently claimed application is directed to a method of identifying a therapeutic process or agent for treating schizophrenia or a related neuropsychiatric disorder involving the dopamine D4 receptor. The method includes using a cultured cell line that naturally expresses D4 receptors or transfected with the

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D4 receptor gene and determining the level of phospholipid methylation upon administration of candidate therapeutic process or agent to cells and making a determination of the phospholipid methylation in the cells. An increase in the level of phospholipid methylation indicates that the agent is potentially therapeutically effective for treating schizophrenia or related neuropsychiatric disorders.

Applicant submits that at the time of the filing of the application, those of ordinary skill in the art would have known from the published literature that neuropsychiatric disorders other than schizophrenia involved dopamine D4 receptor-mediated phospholipid methylation. Applicant provides herein a Declaration under 37 C.F.R. §1.132 by Dr. Richard C. Deth as a supplement to this response. The Deth Declaration supports the inference that an ordinary skilled artisan would reasonably believe based on the specification and on common knowledge that there is a sufficient link between phospholipid methylation and the dopamine D4 receptor in neuropsychiatric disorders other than schizophrenia that the method of the invention would apply.

As described in the Deth Declaration, exemplary neuropsychiatric disorders where dopamine D4 receptor-mediated phospholipid methylation is involved include, for example, autism, attention-deficit hyperactivity disorder and Alzheimer's disease. Autism can effect adenosylsuccinate lyase (ASL) enzyme in the purine synthesis pathway by genetic mutations. As explained, such impairment causes single-carbon groups from the folate pathway to be preferentially diverted toward purine synthesis, resulting in a deficit in the availability of methyl THF for folate-dependent methylation of homocysteine or for folate-dependent methylation of the dopamine D4 receptor (D4R). (*See* Deth Declaration, Paragraph

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7.) Such ASL mutations impair D4R-mediated phospholipid methylation and impair other methylation reactions such as DNA methylation. Here, as the Deth Declaration states, the published literature shows that there is a link between autism and D4R-mediated phospholipid methylation.

Another exemplary neuropsychiatric disorder is attention-deficit hyperactivity disorder (ADHD). ADHD is a widely known disorder in dopamine signaling. D4R is also known to be linked to ADHD (*see* Deth Declaration, ¶8). Therefore, it is reasonable to conclude that dopamine D4 receptor-mediated phospholipid methylation is related to ADHD.

Another exemplary neuropsychiatric disorder is Alzheimer's disease. As explained in Deth Declaration, ¶9, Alzheimer's disease is associated with reduced levels of vitamin B-12 which is the required co-factor for methionine synthase that brings methyl groups from the folate pathway to the D4 dopamine receptor. The enzyme activity of methionine adenosyltransferase, required in the cycle of D4 dopamine receptor-mediated PLM, is also reduced in Alzheimer's disease. Here, again, a link has been shown associating a "related" neuropsychiatric disorder and D4R-mediated phospholipid methylation.

Based on the foregoing descriptions of exemplary neuropsychiatric disorders and their relationship to dopamine D4 receptor-mediated phospholipid methylation, Applicant believes that the specification in combination with common knowledge has been shown to be enabling for neuropsychiatric disorders other than schizophrenia. Undue experimentation will, therefore, not be required.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the foregoing rejection.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that the present application is in condition for allowance.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application : Deth, Richard C.
Application No. : 09/550,103
Filed : April 14, 2000
For : METHODS OF IDENTIFYING AND DETERMINING THE EFFECTIVENESS OF THERAPEUTIC PROCESSES OR AGENTS FOR THE DIAGNOSIS AND TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS
Examiner : Sandra Wegert
Attorney's Docket : NU-431AX

Group Art Unit: 1647

* *

I hereby certify that this correspondence is being sent via facsimile to Examiner Sandra L. Wegert, Group Art Unit 1647, Fax No. (703) 308-4242, on Mar. 3, 2003.

By: Holliday C. Heine
Holliday C. Heine, Ph.D.
Registration No. 34,346
Attorney for Applicant(s)

* *

DECLARATION OF RICHARD C. DETH, PH.D.
UNDER 37 C.F.R. §1.132

Via Facsimile
Commissioner for Patents
Washington, D.C. 20231

I, Richard C. Deth, Ph.D., a citizen of the United States of America, residing at 1484 Beacon Street, Waban, Massachusetts 02468, declare the following:

1. I received my doctoral degree in Pharmacology from the University of Miami (Florida) in 1975. I am currently a Professor of Pharmacology at Northeastern University in Boston, Massachusetts.

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2. I specialize in the study of signaling pathways involving G protein-coupled receptors such as the D4 dopamine receptor. My particular interest is focused on folate-dependent methylation reactions, their control by dopamine and growth factors, and their involvement in various mental illnesses.

3. I am an inventor of the subject matter set forth in the present, above-identified patent application.

4. I have read and am familiar with the prosecution history of the present application, including the Office Action dated October 2, 2002 (Paper No. 9).

5. The detailed action of the Office Action rejects claims 5-9 under 35 U.S.C. §112, first paragraph, because "the specification, while being enabling for a method identifying therapeutic agents for neuropsychiatric diseases involving the D4 receptor and in which phospholipid methylation has been shown to be affected, does not reasonably provide enablement for agents or processes involving other neuropsychiatric disease in which a clear link from the D4 receptor to phospholipid methylation has not been established."

6. This declaration provides support that the specification is enabling for agents or processes involving neuropsychiatric disorders, other than schizophrenia, in which there is a link from the D4 receptor to phospholipid methylation and that it was known at the time of the filing of the application. Herein below are descriptions of exemplary neuropsychiatric disorders where they involve D4 receptor-dependent phospholipid methylation.

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7. An exemplary neuropsychiatric disorder is autism. Autism can be caused by genetic mutations that impair adenosylsuccinate lyase (ASL) enzyme in the purine synthesis pathway (1,2). Such impairment causes single-carbon groups from the folate pathway to be preferentially diverted toward purine synthesis, resulting in a deficit in the availability of methyl THF for folate-dependent methylation of homocysteine or for folate-dependent methylation of the dopamine D4 receptor (D4R). Thus, ASL mutations will impair D4R-mediated phospholipid methylation and will also impair other methylation reactions such as DNA methylation. These latter effects produce the symptoms of autism. Another developmental disorder, Lesch-Nyhan syndrome is also associated with excessive activity of the purine synthesis pathway (3). Additional developmental disorders, including Fragile-X syndrome (4), and Angelman and Prader-Willi Syndromes (4) involve abnormal DNA methylation and gene silencing. Thus developmental disorders as a group appear to involve abnormal folate-dependent methylation events, linking them to folate-dependent D4 receptor-dependent phospholipid methylation. Furthermore, adenosine combines with homocysteine to form S-adenosylhomocysteine (SAH), which functions as an inhibitor of methylation reactions, including DNA methylation. Increased adenosine levels will therefore have an adverse effect on methylation reactions, including folate-dependent D4 receptor-mediated phopsholipid methylation. A decrease in the activity of adenosine deaminase (ADA) has been reported to be associated with autism (6), which would increase adenosine levels and lead to inhibition of methylation. This provides another link between

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methylation and autism and illustrates how autism is a "related psychiatric disorder."

8. One of the hallmark symptoms of autism is impaired attention. This includes attention to other persons as well as impairment of attention-related learning (7). This symptom is also common in schizophrenia (8) and, of course, attention-deficit hyperactivity disorder (ADHD). D4 dopamine receptors have been linked to the risk of attention-deficit hyperactivity disorder (9), so diseases in which there is a deficit of attention are likely to be related to D4 receptor-mediated phospholipid methylation (PLM). ADHD is widely recognized as a disorder of dopamine signaling (10). It is therefore reasonable to conclude that dopamine D4 receptor-mediated PLM is related to ADHD. As noted above, genetic differences in the D4 dopamine receptor have been linked to the risk of ADHD (9). Thus, ADHD may be considered as being related to D4 receptor-mediated PLM, since PLM is a unique functional capacity of the D4 receptor. Animal models of impaired attention have been suggested to be useful for the study of schizophrenia (12). Thus attention-deficit hyperactivity disorder can be considered as being a "schizophrenia-related disorder," since both disorders may include an important role for D4 dopamine receptor-mediated PLM.

9. Alzheimer's disease is associated with reduced levels of vitamin B-12 (12,13), the required co-factor for methionine synthase that brings methyl groups from the folate pathway to the D4 dopamine receptor. Treatment with 5-methylTHF, the source of methyl groups for the D4 receptor PLM process was shown to improve dementia (14). Levels of S-adenosylmethionine, a methyl donor,

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are lower in Alzheimer's disease (15). The enzyme activity of methionine adenosyltransferase, required in the cycle of D4 dopamine receptor-mediated PLM, is reduced in Alzheimer's disease (16). Thus there is considerable evidence for impairments that involve D4 receptor-mediated PLM in Alzheimer's disease, such that it should also be considered as a "related psychiatric disorder."

10. Based on the foregoing, other studies and what is generally known in the art show that there is a reasonable correlation between D4 receptor and phospholipid methylation with other neuropsychiatric disorders. The state of the art at the time of filing indicates that neuropsychiatric disorders, in general, involve phospholipid methylation and the dopamine D4 receptor.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code, and that such willful false statements so made may jeopardize the validity of the document, or application, or any patent issuing thereon.

Signed this 28th day of FEBRUARY, 2003.

By: Richard C. Deth
Richard C. Deth, Ph.D.

Enclosure: List of Cited References (Attached Hereto)

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